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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,680	05/26/2000	Blake R. Pepinsky	BIIJ-P02-067	8259

28120 7590 04/22/2002

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EXAMINER
O HARA, EILEEN B

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/22/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,680	PEPINSKY ET AL.	
	Examiner	Art Unit	
	Eileen B. O'Hara	1646	

-- The MAILING DATE of this communication appears on the c ver sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *19,22-27,34,35,39,47,49,60,61 and 90-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,14,15,28-31,40-42,46,48,50,53,56,57,62-68,71,87-89 and 93-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1-10,14,15,19,22-31,34,35,39-42,46-50,53,56,57,60-68,71 and 87-104.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 1-10,14,15,19,22-31,34,35,39-42,46-50,53,56,57,60-68,71 and 87-104.

DETAILED ACTION

Advisory Information

1. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). The original claims as filed were from 1-86. In preliminary amendment A, Paper No. 10, filed Dec. 31, 2001 (mailed by Applicants on Oct. 24, 2001), claims 87, 88 and 90-105 were added. There was no claim 89. Therefore, misnumbered claims 90-105 been renumbered 89-104. Applicant is reminded that newly numbered claims 91 and 92 now depend from claim 90 instead of claim 91, newly numbered claims 95-99, 101 and 103 now depend from claim 93 instead of 94, newly numbered claim 100 depends from claims 96 and 99 instead of 97 and 100, newly numbered claim 102 depends from claim 95 instead of 96, and newly numbered claim 104 now depends from claim 103.

Status of Claims

2. Claims 1-10, 14, 15, 19, 22-31, 34, 35, 39-42, 46-50, 53, 56, 57, 60-68, 71 and 87-104 are pending in the instant application. Claims 1-10, 15, 25, 27-31, 34, 39, 40, 46, 49, 50, 53, 56, 57, 66-68 and 71 have been amended, claims 11-13, 16-18, 20, 21, 32, 33, 36-38, 43-45, 51, 52, 54, 55, 58, 59, 69, 70, 72-86 have been canceled and claims 87-104 have been added as requested by Applicant in Paper Number 10, filed Dec. 31, 2001.

Election/Restrictions

3. Applicant's election with traverse of Group I in Paper No. 13 is acknowledged. The traversal is on the ground(s) that claims 1-27 encompass overlapping subject matter based on proteins appended with hydrophobic moieties, and thus Groups I and II could be examined simultaneously without significant additional burden. This is not found persuasive because Consistent with current patent practice, a serious search burden may be established by (A) separate classification thereof: (B) a separate status in the art when they are classifiable together:(C) a different field of search:. The two inventions, though related, would require non-coextensive literature searches. Further, a search is directed not only to art which would be anticipatory, but also to art that would render the invention obvious. Thus, the groups require divergent searches, and to search both inventions would be burdensome. However, Group IV, directed to methods for modifying a protein will be rejoined to Group I, since the claimed proteins have to be made using those methods.

The requirement is still deemed proper and is therefore made FINAL.

Claims 90-92, drawn to a method of generating a multivalent protein complex, belong in original Group III, and are drawn to a non-elected invention.

Claims 19, 22-27, 34, 35, 39, 47, 49, 60, 61 and 90-92 are withdrawn as being drawn to a non-elected invention.

Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 62-68, 71, 87-89 and 93-104 are currently under examination.

Information Disclosure Statement

4. The information disclosure statement filed Jan. 16, 2002 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because it states that the list of publications are in the parent application 08/854,039. However, application 08/854,039 is not the parent of this application, which only claims priority benefit from a PCT and four provisional applications. It has been placed in the application file, but the information referred to therein has not been considered as to the merits.

Priority

5. This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior applications. A statement reading "This is a continuation of Application No. PCT/US98/25676, filed December 3, 1997." should be entered following the title of the invention or as the first sentence of the specification. Also, the provisional applications must be included in the statement.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 62-68, 71, 87-89 and 93-104 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3,6,10-18,41-46,48,74,77-79,85 and 94-97 of copending Application No. 09/325,256. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in application 09/325,256 are directed to hydrophobically modified hedgehog proteins (species), while the claims in the instant application are directed to hydrophobically modified proteins that bind a receptor (genus), and the genus is obvious over the species.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Specification

7. The disclosure is objected to because of the following informalities: 0n page 8, in the legend to Fig. 7, (second line) it is stated "soluble (6) and tethered (8) Shh". However, in Fig. 7, there are 7 and not 8 dots that supposedly correspond to tethered Shh.

Appropriate correction is required.

Claim Objections

8. Claim 62 is objected to under 37 CFR 1.75 as being a duplicate of claim 5.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9.1 Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 62-68, 71, 87-89 and 93-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hedgehog proteins that are modified with lipophilic moieties and methods of making them, does not reasonably provide enablement for any other protein that is not a hedgehog protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification teaches that hedgehog proteins from different sources that are modified with a variety of different hydrophobic moieties that are appended to the protein have both increased potency and stability, and is therefore enabled for making and using the modified hedgehog proteins. However, though the specification on page 5 lists a number of other extracellular signaling proteins that can be useful in the invention, there is no working example disclosed in the specification of any other modified protein besides the hedgehog proteins. One of skill in the art would be able to make other proteins having lipophilic moieties since those techniques are old and well known, but the specification does not provide adequate guidance as to any increased potencies or stabilities these proteins would have due to those modifications. It is not disclosed and not predictable from the limited teachings of the prior art and the specification that signaling proteins other than hedgehog proteins that are hydrophobically modified would have increased activity and/or stability. Thus, the specification fails to teach the skilled artisan how to use the claimed polypeptides without resorting to undue experimentation to determine the effect lipophilic modifications would have on the specific biological activities

of the proteins. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the modified proteins.

The discovery that appending hedgehog proteins with different hydrophobic moieties results in increased biological activity does not provide support for the assertion that other signaling molecules that bind to receptors would also have increased activity if appended with hydrophobic moieties for a number of reasons.

First, a major natural form of hedgehog proteins has lipid modifications, and hedgehog proteins expressed and produced from insect cells or mammalian cells have lipid modifications. For example, in insect or mammalian cells sonic hedgehog (Shh) is synthesized as a precursor protein that is cleaved autocatalytically to yield a N-terminal fragment that is responsible for all known hedgehog signaling activity, and a C-terminal fragment that contains the autoprocessing activity. The N-terminal fragment remains membrane-associated through the addition of a cholesterol at its C-terminus, which is catalyzed by the C-terminal domain during the processing step. These cholesterol-modified hedgehog fragments also are appended with palmitic acid at the N-terminal cysteine of the N-terminal fragment, which is added post translation. Therefore, the biologically active form of hedgehog has both a cholesterol moiety and a palmitic acid moiety. The soluble form of the N-terminal fragment of hedgehog lacking the cholesterol and palmitic acid is not as biologically active (about a 30-fold decrease in potency as compared to the lipid modified hedgehog, specification, page 3, lines 5-10). There is no evidence provided in the specification or in the prior art that any other signaling molecule is naturally modified with hydrophobic groups that are necessary for biological activity or that increase activity. The skilled artisan would find it credible that modifying a protein that is naturally modified with hydrophobic moieties and as a result has enhanced activity, with different hydrophobic groups, would also find an enhancement in activity. But no evidence has been provided that modifying a

protein with hydrophobic moieties that normally is not modified as such would increase the proteins activity.

Second, many other signaling molecules (such as insulin, tumor necrosis factor and interferon) are soluble proteins and are not attached to a cell membrane as the hedgehog protein is, and one of ordinary skill in the art would not assume that appending a hydrophobic moiety to such a soluble protein would enhance its biological activity. Additionally, lipid modification appears to be very specific to hedgehog proteins, since in the experiment in example 2 described on page 59-60 of the specification, soluble Shh was labeled with 3H-palmitic acid in a cell-free system using a crude microsomal fraction from rat liver containing hundreds of proteins, yet only the hedgehog protein was labeled (see Fig. 1, lane e for Shh and the corresponding Coomassie blue-stained gel in lane j).

Due to the large quantity of experimentation necessary to determine the specific activities of the proteins, the lack of direction/guidance presented in the specification regarding same, the absence of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention commensurate in scope with the claims. Therefore, the claims are not enabled for proteins other than the hedgehog proteins.

9.2 Claims 1-10, 14, 15, 28-31, 40-42, 46, 48, 50, 53, 56, 57, 62-68, 71, 87-89 and 93-104 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes hedgehog proteins, signaling proteins that bind the patched receptor, that are naturally and artificially modified with hydrophobic moieties which are shown to have enhanced biological activites compared to the non-modified forms.

However, the claims as written include any protein that binds to a receptor that is modified with at least one hydrophobic moiety. The instant disclosure of a single family of proteins, that of hedgehog proteins with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the

genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, that a single family of proteins having similar lipid modifications and activities. Given the unpredictability of the effect of hydrophobic modification on proteins and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. There is no structure set forth for the additional sequences, and there is no correlation or nexus provided between possession of a hydrophobic modification and the encompassed functional features of any protein binding a receptor having enhanced biological activity, such that it is clearly conveyed that possession of any polypeptide having this structural region in common would possess these functional features. Further, even if the proposed modifications and activites were definitive of a genus with a specified function, the instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the proteins encompassed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-10, 14, 15, 62, 68, 87-89 and 93-104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10.1 Claim 1-10, 14, 15 and 62 are indefinite because in claim 1 as written, in the conclusion of the last three lines starting with the phrase "wherein the protein", it is not clear if that refers to just the art of (c) or to the protein in the very beginning of the sentence. One suggestion to clarify the claim would be to replace the phrase "protein is selected from:" on the second line with the phrase "protein has an amino acid sequence selected from:", and replacing "a protein" in parts (a), (b) and (c) with "an amino acid sequence".

10.2 Claims 87 and 88 are indefinite because claim 87 recites the limitation "the hydrophobic moiety", and there is insufficient antecedent basis for this limitation in the claim.

10.3 Claims 68, 87-89 and 93-104 are indefinite because claims 68, 87, 89 and 93 recite "the extracellular receptor", and it is not clear what this term means, if it means a cell-bound receptor that is partially extracellular or if it means a receptor that is not bound to any cell and is completely extracellular.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 3-5, 10, 93, 95-97 and 102 are rejected under 35 U.S.C. 102(b) as being anticipated by Jonassen et al., WO 96/29342, Sept. 26, 1996.

Claims 1, 3-5, 10, 93, 95-97 and 102 encompass a protein in which the N-terminal amino acid or C-terminal amino acid is appended with at least one hydrophobic moiety that is a lipid

that has between 2 and 24 carbon atoms, and that is a signaling protein, and in which the lipid enhances the biological activity of the protein relative to the activity in the absence of the lipid.

Jonassen et al. disclose a peptide hormone derivative (signaling protein that binds receptor) in which the parent hormone has been modified by introducing a lipophilic substituent in the N-terminal amino acid or in the C-terminal amino acid, and in which the lipophilic substituent has from 8-40 carbon atoms, and in which biological activity is enhanced (see abstract, page 3, lines 1-5, page 5, lines 1-11). The protein of Jonassen et al. therefore anticipates the claims.

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

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